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10/049,429	09/08/2003	Joseph Schlessinger	038602-1306	3634

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,429	SCHLESSINGER ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-89* is/are pending in the application.

4a) Of the above claim(s) *13-16,18-68,75 and 77-89* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,17,69-74 and 76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/12/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-89 are pending in the application.

[2] Applicant's response, filed September 24, 2004, to the restriction requirement mailed September 03, 2004, is acknowledged.

Lack of Unity

[3] Applicant's election with traverse of Group I, claims 1-12, 17, 69-74, and 76, is acknowledged. The elected invention is drawn to the special technical feature of a crystal comprising an extracellular domain of a receptor protein tyrosine kinase (RPTK), including fibroblast growth factor receptor 1 (FGFR1), optionally further comprising a ligand bound to the RPTK, wherein the ligand includes fibroblast growth factor 1 (FGF1).

RESPONSE TO TRAVERSE: Applicants argue there is no undue burden to search all of the claims. Applicants' argument is not found persuasive.

To the extent the restriction is made under 35 U.S.C. 121, it is noted that each of the inventions listed as Groups I-XVII requires a separate search, particularly in view of the recitation of limitations that are exclusive to the claims of the invention of Group I. It should be noted that applicants fail to present any line of reasoning or evidence that a co-extensive examination of all claims would not require a serious burden on the examiner.

[4] The requirement is still deemed proper and is therefore made FINAL.

[5] Claims 13-16, 18-68, 75, and 77-89 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on September 24, 2004.

[6] Claims 1-12, 17, 69-74, and 76 are being examined on the merits.

Priority

[7] Applicants' claim to foreign priority under 35 U.S.C. 119(a)-(d) to application PCT/US00/23744, filed August 30, 2000, is acknowledged. However, a foreign priority claim is not necessary as the instant application is the national stage of PCT/US00/23744 and applicants are afforded priority to the filing date of that international application.

Applicants' claim to domestic priority under 35 U.S.C. 119(e) to provisional application 60/151,810, filed August 30, 1999, is acknowledged.

Information Disclosure Statement

[8] All references cited in the IDS filed March 21, 2002 have been considered by the examiner. A copy of the IDS is attached to the instant Office action.

Oath/Declaration

[9] The objection to the Declaration is maintained for the reasons of record as set forth at item [4] of the Office action mailed September 03, 2004 and for the reasons stated below.

RESPONSE TO ARGUMENTS: Applicants argue a replacement declaration is not required as inventor Mohammadi has signed and dated below the crossed out text on the same page. Applicants' argument is not found persuasive.

Applicants' attention is directed to MPEP 605.049(a), which states, "[a]ny changes made in ink in the application or oath prior to signing should be initialed and dated by the applicants prior to execution of the oath or declaration" and that "[t]he Office will not consider whether noninitialed and/or nondated alterations were made before or after signing of the oath or declaration but will require a new oath or declaration." As such, a new oath or declaration in compliance with 37 CFR 1.67(a) is required.

Request for Clarification

[10] It is unclear to the examiner as to which sequence in the paper copy of the sequence listing has the amino acid sequence of FGF1 as shown in Figure 17. SEQ ID NO:17 appears to have the same amino acid sequence as that shown for FGF1 in Figure 17 and the claims have been examined accordingly. Clarification is requested.

Sequence Compliance

[11] This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). See particularly Figures 4, 15, 17, 20, and 25.

Specification/Informalities

[12] The attempt to incorporate subject matter into this application by reference to a hyperlink embedded in the specification (for example, page 95, bottom) is improper. Incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper

incorporation by reference. See MPEP 608.01 regarding hyperlinks in the specification and 608.01(p), paragraph I regarding incorporation by reference. Due to the sizable length of the specification, applicants' cooperation is requested in locating other hyperlinks and making the appropriate correction(s).

[13] The use of the trademarks "Centricon 10" and "Superdex 200" has been noted in this application (p. 89 of the specification). They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. Due to the sizable length of the specification, applicants' cooperation is requested in locating other trademarks and making the appropriate correction(s).

[14] The description of Figure 4 (p. 27) does not correspond to the drawing of Figure 4 as Figure 4 shows the amino acid sequences of FGFRs, while the description of Figure 4 indicates that the amino acid sequences are those of FGFs. Appropriate correction is required.

Claim Objection(s)

[15] Claim 6 is grammatically incorrect in the recitation of "wherein polypeptide" and should be amended to recite "wherein the polypeptide."

[16] Claims 7, 9-10, and 74 are objected to because of the recitation of "FGFR1," "FGF1," "FGF," and "FGFR." Abbreviations, unless otherwise obvious, should not be

recited in the claims without at least once reciting the entire phrase for which the abbreviation is used, *e.g.,* fibroblast growth factor receptor 1 (FGFR1).

[17] Claims 7 and 10 are objected to as referring to sequences without the use of a sequence identifier. 37 CFR 1.821(d) states, "[w]here the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application."

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[18] Claims 1-6, 8-9, 12, 17, 69-74, and 76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claims 1 (claim 17 dependent therefrom), 2-6, 8-9, 17, 69, 70 (claim 71-73 dependent therefrom), 74, and 76 are indefinite in the recitation of "extracellular domain" (claims 1, 2, 4, and 69), "receptor protein tyrosine kinase" (claims 1, 3, 8, 69-70, and 76), "Ig-like domains" or "Ig-like domain" (claims 2 and 4), "fibroblast growth factor receptor," "fibroblast growth factor receptor 1," "FGFR," or "FGFR1" (claims 3, 5-6, 9,

74, and 76), "fibroblast growth factor," "FGF," or "FGF1" (claims 9, 74, and 76) as it unclear as to the scope of amino acid sequences that are intended to be encompassed by the terms stated above such that one of skill in the art can distinguish the intended polypeptide sequences from those that are not intended to be encompassed by the scope of the claims. In other words, how does one distinguish an extracellular domain of a receptor protein tyrosine kinase, a receptor protein tyrosine kinase, an Ig-like domain, a fibroblast growth factor receptor, or a fibroblast growth factor from any other respective extracellular domains of a receptor protein tyrosine kinase, receptor protein tyrosine kinases, Ig-like domains, fibroblast growth factor receptors, or fibroblast growth factors? While it is noted that the terms "RPTK," "FGFR1," "extracellular domain," and "fibroblast growth factor" are "defined" in the specification (pp. 5-6), however, these "definitions" fail to clearly define the scope of intended extracellular domains of a receptor protein tyrosine kinase, receptor protein tyrosine kinases, fibroblast growth factor receptors, or fibroblast growth factors as recited in the claims.

[b] Claims 2 (claim 3 dependent therefrom) and 4 are indefinite in the recitation of "Ig-like" as it is unclear as to how "Ig-like" a domain must be to included within the scope of the recited "Ig-like" domains. It is suggested that applicants clarify the meaning of the term.

[c] Claim 5 recites the limitation "the fibroblast growth factor receptor" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

[d] Claim 6 is indefinite in the recitation of "amino acid residues 142-365 of fibroblast growth factor receptor 1" as it is unclear as to the reference amino acid sequence of

fibroblast growth factor receptor 1 to which applicants refer. It is suggested that applicants clarify the meaning of the claim by the use of a sequence identifier as a reference sequence for identifying amino acids 142-365.

[e] Claim 10 is indefinite in the recitation of "FGF1 has an amino acid sequence as shown in Figure 17" as Figure 17 lists numerous amino acid sequences. It is suggested that the amino acid sequence of FGF1 be specifically identified, *e.g.,* by use of a sequence identifier.

[f] Claim 12 is confusing in that the claim is drawn to a crystal of FGFR1 complexed with FGF1 having tetragonal space group P1 and unit cell dimensions of a=b=98.5 Δ and c=197.0 Δ. However, the only disclosed crystal having unit cell dimensions of a=b=98.5 Δ and c=197.0 Δ is a crystal of FGFR1 complexed with FGF2. Applicants are requested to clarify the meaning of the claim.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

[19] Claims 5-7 and 9-12 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or well-established utility. The claims are drawn to crystals of FGFR1 optionally complexed with FGF1.

The specification asserts the crystal of FGFR1 complexed with FGF1 can be used to generate a three-dimensional structure for use in determining binding agents such as therapeutic molecules. However, the specification fails to teach an association between FGFR1 and a particular disease that can be therapeutically treated using a compound that binds to FGFR1. While it is acknowledged that the specification asserts that mutations in the gene encoding FGFR1 have been "implicated" in a genetic skeletal disorder (p. 39), there is no indication that such genetic disorder can be treated using an FGFR1 binding agent. As such, further experimentation is required to determine a "real world" use for the claimed invention. See Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966). The specification must teach a skilled artisan how to use what is claimed and not merely provide a blueprint for further experimentation in order for an artisan to identify a use for the claimed invention. As stated in Brenner v. Manson, 383 U.S. 519 535-536, 148 USPQ 689, 696 (1966), "[a] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion".

[20] Claims 5-7 and 9-12 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[21] Claim(s) 1-12, 17, 69-74, and 76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a genus of crystals of an RPTK optionally complexed with a ligand, wherein the RPTK is optionally FGFR or FGFR1 and the ligand is optionally FGF or FGF1. For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of the genus of claimed crystals of FGFR1 in complex with FGF1, *i.e.,* a crystal of the purified polypeptide of SEQ ID NO:1 co-crystallized with the FGF1 of SEQ ID NO:17 having

tetragonal space group symmetry P1 and the unit cell dimensions of a=62.55, b=64.06Δ, c=64.14 Δ, α=93.40°, β=111.17°, and γ=97.18°. The specification fails to describe any additional representative species of the claimed genus. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". In the instant case, the claimed genus of crystals encompasses species that are widely variant in the structures of the RPTK, including mutant and variant RPTKs (p. 41, lines 11-12), the ligand bound to the RPTK, and the physical characteristics of the resulting crystal. As such, the disclosure of the single representative species is insufficient to be representative of the attributes and features of *all* species encompassed by the claimed genus of claimed crystals. Given the lack of description of a representative number of crystals, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[22] Even if applicants' demonstrate a specific and substantial or well-established utility for the crystal of claims 5-7 and 9-12, the following rejection applies to those claims. Claim(s) 1-12, 17, 69-74, and 76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a crystal of the purified polypeptide of SEQ ID NO:1 co-crystallized with the FGF1 of SEQ ID NO:17 having tetragonal space group symmetry P1 and the unit cell dimensions of a=62.55,

b=64.06Δ, c=64.14 Δ, α=93.40°, β=111.17°, and γ=97.18°, does not reasonably provide enablement for the broad scope of crystals as encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: The claims are so broad as to encompass all crystals of a polypeptide that includes an extracellular domain of an RPTK, including any FGFR, mutants and variants thereof (p. 41, lines 11-12), optionally complexed with any ligand, including any FGF. However, the enablement provided by the disclosure in view of the prior art is not commensurate in scope with the claimed invention. In this case the disclosure is limited to a crystal of the purified polypeptide of SEQ ID NO:1 co-

crystallized with the FGF1 of SEQ ID NO:17 having tetragonal space group symmetry P1 and the unit cell dimensions of a=62.55, b=64.06Δ, c=64.14 Δ, α=93.40°, β=111.17°, and γ=97.18°.

- The lack of guidance and working examples: The specification provides only a single working example of the claimed crystal of FGFR1 liganded with FGF, a crystal of the purified polypeptide of SEQ ID NO:1 co-crystallized with the FGF1 of SEQ ID NO:17 having tetragonal space group symmetry P1 and the unit cell dimensions of a=62.55, b=64.06Δ, c=64.14 Δ, α=93.40°, β=111.17°, and γ=97.18°. This single working example fails to provide the necessary guidance for making the entire scope of crystals broadly encompassed by the claims. The specification fails to provide guidance regarding crystallization of FGFR1 polypeptides optionally complexed with a ligand other than a crystal of SEQ ID NO:1 in complex with SEQ ID NO:17 having tetragonal space group symmetry P1 and the unit cell dimensions of a=62.55, b=64.06Δ, c=64.14 Δ, α=93.40°, β=111.17°, and γ=97.18°, *e.g.,* crystals of mutants and variants of the FGFR1 of SEQ ID NO:1, splice variants of FGFR1 optionally complexed with any other ligand, *e.g.,* mutants and variants of the FGF1 of SEQ ID NO:17.

- The high level of unpredictability in the art: The state of the art at the time of the invention acknowledges a high level of unpredictability for making the full scope of claimed crystals. For example, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "[c]rystallization is usually quite difficult to achieve" (p. 375). In view of the use of the

claimed crystal for generating a three-dimensional structure, it is noted that the claimed crystals should be of diffraction quality, having a well-ordered structure. Branden et al. teaches that "[w]ell-ordered crystals... are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Further, Branden et al. teaches the formation of protein crystals is critically dependent on a number of different parameters, including pH, temperature, protein concentration, the nature of the solvent and precipitant, as well as the presence of added ions and ligands to the protein (page 375). Branden et al. teach that even small changes in the crystallization parameters can cause the molecules to pack in different ways to produce different crystal forms (page 375, bottom). Thus, even minor modifications to a crystallization method may result in crystals that are distinct in structure having different space group symmetry and unit cell dimensions. Applicants' own specification exemplifies the teachings of Branden et al., as the crystals of FGFR1-FGF1, FGFR1-FGF2, and FGFR2-FGF2 all have distinct space group symmetries and/or unit cell dimensions (p. 11).

- The amount of experimentation required is undue: While methods of protein crystallization are known, it is *not* routine in the art to crystallize a vast number proteins optionally complexed with any ligand under any crystallization conditions to make all crystals as broadly encompassed by the claims.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high degree of unpredictability as evidenced

by the prior art, and the amount of experimentation required to make all crystals as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

[23] Claims 1-2, 8, and 69 are rejected under 35 U.S.C. 102(b) as being anticipated by Wiesmann et al. (*Cell* 91:695-704). The claims are drawn to a crystal of an extracellular domain of an RPTK optionally complexed with a ligand.

Wiesmann et al. teach a crystal of extracellular immunoglobulin domain 2 of Fms-like tyrosine kinase complexed with vascular endothelial growth factor (p. 695, abstract, and p. 702). This anticipates claims 1-2, 8, and 69 as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[24] Claim(s) 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wiesmann et al. in view of the state of the art at the time of the invention. Claim 17 limits the crystal of claim 1 to a crystal comprising at least one heavy atom.

Wiesmann et al. disclose the crystal as described above.

Also, at the time of the invention, the use of heavy atom replacement for crystallization and X-ray diffraction was well-known and established in the art for improving structural resolution. One merely need recombinantly produce a protein in the absence of a defined medium comprising a heavy atom amino acid derivative, *e.g.,* selenomethionine, and crystallize the resulting protein.

Therefore, it would have been obvious to one of ordinary skill in the art to recombinantly produce a heavy atom derivative of Flt-1 and/or VEGF and crystallize the resulting complex. One would have been motivated to crystallize a heavy atom

derivative of Flt-1 and/or VEGF in order to improve the resolution of the crystal structure. One would have a reasonable expectation of success for recombinantly producing a heavy atom derivative of Flt-1 and/or VEGF and crystallizing the resulting complex because of the results of Wiesmann et al. and the state of the art at the time of the invention. Therefore, claim 17, drawn to a crystal as described above would have been obvious to one of ordinary skill in the art.

Conclusion

[25] Status of the claims:

- Claims 1-89 are pending.
- Claims 13-16, 18-68, 75, and 77-89 are withdrawn from further consideration.
- Claims 1-12, 17, 69-74, and 76 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Thursday from 7:30 am to 5:00 pm and from 7:30 am to 4:00 pm on alternate Fridays. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

6-1-05

David J. Steadman
Primary Examiner
Art Unit 1652